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RESEARCH ARTICLE

Warfarin Induced Coagulopathy- Prevalence, Risk Factors and Correlation of Bleeding Severity with INR Values - A Cross-sectional Study

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Abstract

Background: Warfarin, a commonly used oral anticoagulant, is associated with a significant risk of bleeding due to its narrow therapeutic index and multiple patient-specific influencing factors. Understanding the prevalence, severity, and predictors of bleeding is essential for optimizing patient safety. **Aim and Objective:** To determine the prevalence of bleeding among patients on Warfarin therapy and to identify risk factors for major and minor bleeding, with a focus on correlating bleeding severity with INR values. **Materials and Methods:** A hospital-based cross-sectional study was conducted over 3 months at the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, Chennai. A total of 76 adult patients on Warfarin (Acitrom) for at least three months were enrolled consecutively. Clinical history, concomitant medication usage, and INR levels were documented. Bleeding manifestations were assessed and classified as mild, moderate or severe. Laboratory investigations and imaging were performed as needed. Statistical analysis was done using SPSS v23, with a p-value <0.05 considered significant. **Results:** The prevalence of Warfarin-induced bleeding was 47.3% (n=36). Bleeding was significantly more common in females (p=0.003). Among those with bleeding (n=36), 52.45% were on 6-12 concomitant medications. Severity of bleeding did not show a significant association with gender (p=0.44). The most frequent bleeding sites were gastrointestinal (34.42%) and skin/ecchymosis (29.51%). Polypharmacy and female gender were identified as key predictors of bleeding. **Conclusion:** Nearly half of the patients on Warfarin therapy experienced bleeding complications, with female sex and polypharmacy being significant risk factors. Regular INR monitoring and minimization of concomitant medications are crucial to reduce bleeding risk. Clinicians must remain alert to bleeding signs, particularly in the gastrointestinal and cutaneous systems, to ensure prompt intervention.

Keywords: Anticoagulation, Bleeding, Cross-sectional Study, INR, Polypharmacy, Risk Factors, Warfarin

1. Introduction

Warfarin and its derivatives are Vitamin K antagonists that inhibit the activation of Vitamin K dependent clotting factors, hence creating an anticoagulant state in the body. Warfarin, like many other anticoagulants, has been linked to an elevated risk of bleeding proportional to the amount of anticoagulation used[1]. It can be used to prevent thrombosis in people who are at risk for or have experienced thrombotic events in the past. These individuals include people with thrombophilias, cardiac valve replacements, deep vein thrombosis, pulmonary embolism and atrial fibrillation patients who are susceptible to thromboembolism[1,2]. According to numerous studies, the annual incidence of significant bleeding in people using warfarin varies between 0.4% and 7.2%. The annual rate of minor bleeding can reach 15.4%. It is believed that many patient-specific factors that can change metabolism are the cause of this broad range. Furthermore, significant bleeding events were frequently defined differently in previous investigations[2,3].

Warfarin has a narrow therapeutic index; hence, warfarin dosages for each patient rely on various

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criteria, including co-morbidity, compliance, food and drug interactions and alcohol consumption status. Several factors affect warfarin therapy and can cause problems[4]. Bleeding and thromboembolic events occurred when the therapeutic index of warfarin was excessively and inadequately dosed, respectively[4,5]. Bleeding and substantial hemorrhage were serious warfarin complications, such as intracranial hemorrhage, gastrointestinal bleed, ophthalmic bleeding and so on[6]. There were three classifications for major bleeding events: Fatal, major, and minor. Initially, the fatal bleeding complication was the autopsy- or radiologically- or clinically obvious death owing to hemorrhage. Second, the major bleeding complications included intracranial bleeding, retroperitoneal bleeding, intraocular bleeding, spontaneous muscle hematoma associated with compartment syndrome, any invasive procedure to stop bleeding and active bleeding from any orifice in conjunction with unstable vital status[7,8].

2. Aim and Objectives

- To determine the prevalence of bleeding among patients on Warfarin therapy.
- To predict the risk factors for major and minor bleeding with correlation between severity of bleeding and INR values.

3. Review of Literature

Haritha Nekkanti *et al.* the study, which aimed to determine the predictors of warfarin- induced bleeding, involved 235 individuals in total[1]. Only medications that contained warfarin were chosen for the study. To determine if demographics and risk variables were related, the chi square test was employed. The most frequently used medications were aspirin (40.98%), heparin (36.06%), clopidogrel (22.95%), and streptokinase (14.75%). Additionally, this study found that comorbid conditions such as diabetes (37.70%), hypertension (32.78%), smoking (57.37%), and alcohol (32.78%) were significant predictors of warfarin-induced bleeding. The majority of warfarin-induced bleeding responses were moderate in severity (44.26%), with the gastrointestinal tract being the most frequently affected location of bleeding. Female gender, duration of hospitalization, number of medications, aspirin, heparin, and clopidogrel, as well as other comorbidities including smoking, alcohol and hypertension, were revealed to be predictors of warfarin-induced bleeding.

Benyapha Sombat *et al.*[9] the incidence of warfarin complications was 4.91 occurrences per 100 person-year among 335 patients (683.90 person-year of follow-up)[9]. Prescription propranolol was the independent factor linked to warfarin therapy problems (Adjusted RR: 2.29, 95%CI: 1.12-4.71).

Depending on how the significant bleeding and thromboembolic event turned out, the secondary analysis was separated. Among the independent risk variables were major bleeding events, hypertension (Adjusted RR: 0.40, 95%CI: 0.17-0.95), prescriptions for amiodarone (adjusted RR: 5.11, 95% CI: 1.08-24.15), and propranolol (adjusted RR: 2.86, 95% CI: 1.19-6.83). Prescriptions for Non-Steroidal Anti-Inflammatory Medicines (NSAIDs) were an independent risk in the main thrombotic event (adjusted RR: 10.65, 95%CI: 1.26-90.35).

S D Fihn , M McDonell *et al.* at one year and three years, the cumulative incidence of fatal bleeding was 1% and 2%, respectively[10]. At one, two, four of age, and the incidence of Warfarin-associated bleeding observed in our study is consistent with findings from primary care settings. A large population-based study from the United Kingdom by Hollowell et al. reported a substantial burden of bleeding complications among patients receiving Warfarin in routine clinical practice, highlighting the importance of close monitoring even outside tertiary care centers[11]. The cumulative occurrences of the first bouts of serious and potentially fatal bleeding were 1%, 2%, 5%, and 9% and 12%, 20%, 28%, and 40%, respectively. 32% of the 156 patients who experienced a severe or life- threatening hemorrhage experienced another one, usually within a year. A mean Prothrombin Time Ratio (PTR) of 2.0 or higher during treatment (relative risk, 3.0; 95% CI, 1.9 to 4.7); recent initiation of warfarin therapy (relative risk during the first 3 months compared with the remainder of the first year, the second year, and at any time after, 1.9 [CI, 1.3 to 3.0], 3.0 [CI, 1.8 to 4.8], and 5.9 [CI, 3.8 to 9.3], respectively); variability of the PTR over time (relative risk for the highest compared with the lowest tertile, 1.6 [CI, 1.2 to 2.7]); and the presence of three or more comorbid conditions (RR,

1.4 [CI, 1.1 to 2.5]) were independent predictors of a first episode of serious bleeding. The risk of bleeding was not correlated with age, the reason for anticoagulation, the use of interfering medications, or hypertension. When the PTR was less than 1.3, the risk of a thromboembolic complication was 3.6 (CI, 2.1 to 6.4) times greater than when the PTR was between 1.3 and 1.5. By addressing modifiable risk factors (*i.e.*, highly fluctuating PTRs and values more than 2.0), frequent monitoring early in treatment, and cautious patient selection, the incidence of warfarin-associated bleeding may be decreased. Being older is not a risk factor in and of itself.

4. Material and Methods

4.1 Inclusion Criteria

1. Age group above 18 years.
2. Patients who are on Acitrom (Coumarin derivatives) for at least 3 months continuous duration.

4.2 Exclusion Criteria

1. Age <18 years
2. Known bleeding disorder.
3. Patients on concomitant antiplatelet therapy.
4. Patients enrolled in other study.
5. Patients on NOAC therapy.

This prospective study was conducted in the Institute of Internal Medicine, Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai, over a period of three months from the date of ethical committee approval. A total of 76 patients who met the inclusion and exclusion criteria were selected after obtaining informed consent. A detailed clinical history was recorded for each patient, including the indication for initiating warfarin therapy (Acitrom), the duration of therapy and any complications or bleeding manifestations.

Relevant information was also obtained from past medical records. All patients underwent baseline blood investigations, including Prothrombin Time (PT), International Normalized Ratio (INR), and Activated Partial Thromboplastin Time (aPTT), in order to assess their coagulation status and correlate INR levels with the presence and severity of bleeding. Imaging studies such as CT brain, ECG, echocardiography, and Oesophago Gastroduodeno scopy (OGD scopy) were performed depending on the site and nature of the bleeding presentation.

Demographic variables were analyzed to identify potential predictors of bleeding. These factors included patient characteristics such as age (over 18 years), gender, comorbidities, and duration of hospital stay. Drug-related factors such as the number of concomitant medications used along with Acitrom, and the duration of therapy, were also considered. Laboratory findings were integrated into the analysis.

Descriptive statistics, including frequencies and percentages, were used to summarize demographic variables (age, sex), length of stay, number of drugs dispensed, incidence of bleeding, drugs implicated in the bleeding episodes, and associated comorbidities. A case was defined as any individual who experienced bleeding while on warfarin therapy, whether taken alone or in combination with other medications, particularly those known to cause drug-drug interactions. The severity of bleeding was classified into mild, moderate, and severe. Mild bleeding included petechial hemorrhages, minor yet clinically significant blood loss or bleeding episodes that did not necessitate transfusion. Moderate bleeding was characterized by visible or gross blood loss that required blood transfusion. Severe bleeding was identified as life-threatening or debilitating blood loss including retinal, gastrointestinal, or cerebral hemorrhages and those associated with fatal outcomes. All patient data were compiled in a master chart, capturing clinical, demographic, therapeutic, and outcome parameters, which were used for statistical analysis to determine risk factors, correlations and the severity of bleeding manifestations among patients on warfarin therapy.

4.3 Study Period

3 months from Ethical committee approval (July to September 2024).

4.4 Study Design

Cross sectional study- Observational

4.5 Study Population

Participants attending Internal Medicine OPD, and those in admission in medical wards fulfilling the inclusion criteria.

4.6 Sampling Method

4.6.1 Consecutive Sampling Technique

Sample Size Calculation

The sample size for the study was based on a study by Haritha Nekkanti *et al.* in 2010 and the study suggested the proportion of bleeding among the 235-population enrolled in study to be: 25.95%.

The sample size was calculated according to the formula:

N = Zα2pq D2
p = 25.95
q = 74.05
Absolute precision, d = 10

Based on the formula given above, using the mentioned values, the sample size required is: (1.96)2 x 25.95 x 74.05/(10 x 10) = 75.92 (~76).

Thus, with 95% confidence interval, the proposed sample size for the study is 76.

5. Results

The distribution of patients on Warfarin therapy (n = 76) showed that the majority were in the 41–61 years age group (39.4%, n = 30), followed by patients aged above 61 years (30.2%, n = 23) and those aged ≤40 years (25%, n = 19). Females constituted the majority of the study population (76.3%, n = 58), while males accounted for 23.6% (n = 18) (Table 1)

Table 1. Demographic distribution of patients on warfarin therapy (n=76)

Variable	Category	Frequency (n)	Percentage (%)
Age group	≤40 years	19	25%
	41–61 years	30	39.4%
	>61 years	23	30.2%
Gender	Male	18	23.6%
	Female	58	76.3%

Table 2. Prevalence of warfarin-induced bleeding (n=76)

Bleeding Status	Frequency (n)	Percentage (%)
Bleeding present	36	47.3%
No bleeding	40	52.6%

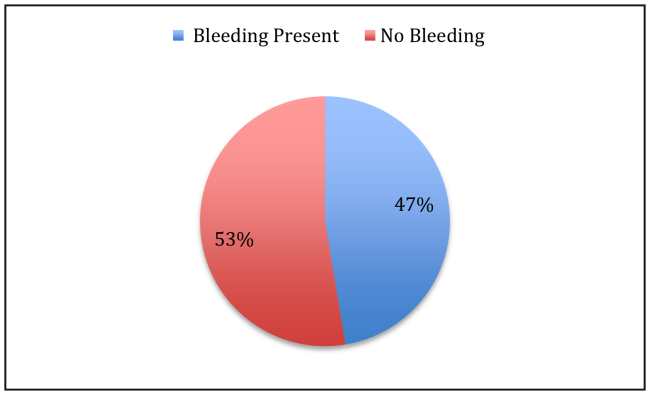

Figure 1. Prevalence of warfarin-induced bleeding.

Table 3. Number of concomitant medications in patients with bleeding (61)

Number of Drugs	Frequency (n)	Percentage (%)
≤5	15	24.59%
6–12	32	52.45%
>12	14	22.95%

The prevalence of Warfarin-induced bleeding was observed in 47.3% (n = 36) of patients, while 52.6% (n = 40) did not exhibit any bleeding manifestations (Table 2, Figure 1)

Among patients who experienced bleeding, 52.45% (n = 32) were taking 6–12 concomitant medications, 24.59% (n = 15) were on five or fewer drugs, and 22.95% (n = 14) were taking more than 12 medications, indicating a strong association between polypharmacy and bleeding risk (Table 3)

When severity of bleeding was analyzed according to gender, mild bleeding was noted in 6 males and 8 females, moderate bleeding in 10 males and 22 females, and severe bleeding in 14 males and 16 females. The association between severity of bleeding and gender was not statistically significant (p = 0.44). However, bleeding episodes were significantly more common in females compared to males (p = 0.003) (Table 4)

Regarding the site of bleeding, the gastrointestinal tract was the most common site (34.42%), followed by skin/ecchymosis (29.51%), genitourinary tract (16.39%), oral/nasal bleeding (11.48%), and intracranial hemorrhage (8.20%) (Table 5, Figure 2)

The patients who experienced Warfarin-induced bleeding, the most common site of bleeding was the gastrointestinal tract, accounting for 34.42% (n=21) of cases. This was followed by skin-related bleeding

Table 4. Severity of warfarin-induced bleeding

Severity	Frequency		Chi-square	p-value
	Male	Female		
Mild	6	8	1.642	0.44
Moderate	10	22		
Severe	14	16		
Bleeding	13	23	8.858	0.003
Non bleeding	28	12		

Table 5. Risk of bleeding in warfarin-induced bleeding cases (n=61)

Site of Bleeding	Frequency (n)	Percentage (%)
Gastrointestinal	21	34.42%
Genitourinary	10	16.39%
Oral/Nasal	7	11.48%
Intracranial	5	8.20%
Skin/Ecchymosis	18	29.51%

manifestations such as ecchymosis, seen in 29.51% (n=18) of patients. Genitourinary bleeding occurred in 16.39% (n=10), while oral or nasal bleeding was reported in 11.48% (n=7). Intracranial bleeding, although less frequent, was present in 8.20% (n=5) of the cases. These findings highlight the gastrointestinal and skin as the predominant bleeding sites in Warfarin-treated patients.

6. Discussion

In the present study involving 76 patients on Warfarin therapy, the prevalence of bleeding was observed in 47.3% of patients. This finding is consistent with previously published literature. For instance, Ghaswalla *et al.*[12] reported a similar prevalence of bleeding complications among patients on oral anticoagulation, particularly in high-risk groups. Another study by Holbrook *et al.*[13] highlighted that nearly one-third to half of the patients on Warfarin therapy develop some form of bleeding, emphasizing the narrow therapeutic index of the drug.

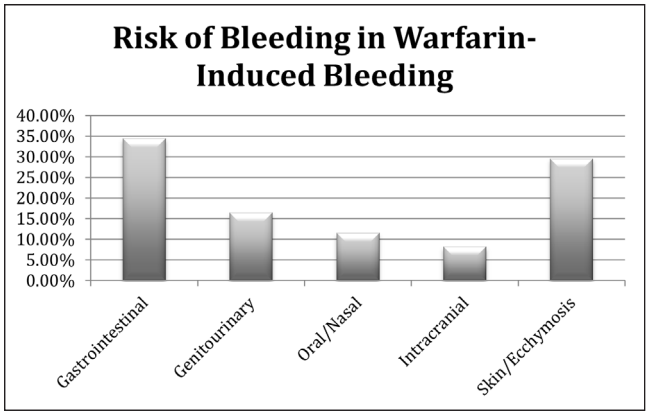

Figure 2. Risk of bleeding in warfarin-induced bleeding.

When analyzing gender differences, bleeding was more commonly observed in females (n=23) than males (n=13), and this association was statistically significant (p = 0.003). Similar findings were reported by Fang *et al.*[14] who noted a higher bleeding risk in female patients on Warfarin, possibly due to differences in pharmacokinetics and body composition. However, the severity of bleeding (mild, moderate, severe) did not show a significant difference across gender (p = 0.44), suggesting that while females may bleed more frequently; the intensity of bleeding may not necessarily be worse compared to males.

The number of concomitant medications was found to play a critical role in bleeding risk. Over half (52.45%) of the patients with bleeding were taking between 6-12 additional drugs. Polypharmacy is a well-established risk factor for anticoagulant-related bleeding, as many drugs interact with Warfarin either by displacing it from plasma proteins or altering its metabolism (Routledge *et al.*)[15]. This highlights the need for careful review of concurrent medications in patients receiving Warfarin.

Regarding the site of bleeding, the gastrointestinal tract was the most common site (34.42%), followed by skin/ecchymosis (29.51%), genitourinary tract (16.39%), oral/nasal mucosa (11.48%), and intracranial sites (8.20%). These findings align with data from Kaatz *et al.*[16] who reported gastrointestinal bleeding as the leading cause of clinically significant Warfarin-related hemorrhage, due to the high vascularity and mucosal fragility of the GI tract. Skin bleeding, often in the form of ecchymosis or bruising, is a common minor manifestation, especially in elderly patients with fragile capillaries (Ansell *et al.*)[17].

The risk of intracranial hemorrhage, though lower in frequency (8.20%), is particularly concerning due to its high morbidity and mortality. According to a meta-analysis by Aguilar and Hart, Warfarin-associated

intracranial hemorrhage remains one of the most feared complications, especially in those with poorly controlled INR values or underlying cerebrovascular risk factors[18].

7. Summary and Conclusion

This cross-sectional study conducted at a tertiary care center in Chennai assessed the prevalence, severity, and risk factors associated with Warfarin-induced bleeding among 76 patients on Warfarin therapy for at least three months. The study found that 47.3% of the participants experienced bleeding complications, with a significantly higher incidence among females (p=0.003). Over half of the bleeding cases were associated with moderate polypharmacy, where patients were taking between 6-12 concomitant medications. Although the severity of bleeding (classified as mild, moderate, or severe) did not significantly differ by gender (p=0.44), the overall bleeding burden was higher in female patients. The most common bleeding sites were the gastrointestinal tract (34.42%) and skin/ecchymosis (29.51%). These findings highlight the importance of individualized Warfarin dosing, close INR monitoring, and minimizing concurrent drug usage to reduce bleeding risks. Regular clinical vigilance is especially warranted in females and patients on multiple medications to ensure safer anticoagulation therapy.

This cross-sectional study provides important insights into the bleeding risk associated with Warfarin (Acitrom) therapy in a tertiary care setting. The findings reveal a high prevalence of bleeding (47.3%), with a statistically significant association with female gender (p=0.003) and polypharmacy, particularly in patients taking 6-12 concurrent medications. Although severity of bleeding (mild/moderate/severe) did not significantly differ by gender, the overall burden of bleeding was higher in females. The most common bleeding sites were gastrointestinal and skin/ecchymosis, highlighting the need for targeted monitoring.

The study emphasizes the critical need for individualized Warfarin dosing, regular INR surveillance, and minimizing drug interactions. Healthcare providers must exercise caution when prescribing Warfarin, especially in patients with multiple comorbidities and those receiving numerous concomitant medications. Early identification of bleeding manifestations and appropriate dose adjustments can greatly reduce the risk of serious complications.

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